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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/503,596	02/11/2000	Mu-en Lee	05433-042001	6895

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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	18

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/503,596	Applicant(s) LEE ET AL.	
	Examiner Mary M. Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6 and 9-25* is/are pending in the application.

4a) Of the above claim(s) *13-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9-12,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 February 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: See the PTO-948 provided with the Office action mailed 8/14/02 for objections to drawings.

DETAILED ACTION

1. Claims 13-23 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11, filed 9/10/01.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3, 5-6, 9-12 and 24-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons of record as set forth in the Official Action mailed 11/23/01.

Applicant's arguments filed 2/14/03 have been fully considered but they are not persuasive.

Claim 1 as amended is drawn to a method of inhibiting formation of an atherosclerotic lesion comprising administering to a mammal a compound that reduces expression of AFABP,

wherein said AFABP comprises the amino acid sequence of SEQ ID NO:4 and wherein a reduction in AFABP expression inhibits formation of an atherosclerotic lesion and wherein said compound comprises an nucleic acid comprising 10-100 nucleotides, the sequence of said nucleotides being complementary to a coding sequence of SEQ ID NO:2.

Claim 2 as amended is drawn to a method of inhibiting formation of an atherosclerotic lesion in a mammal, comprising identifying a mammal in need of said inhibition, and introducing to said mammal a compound that reduces expression of AFABP, wherein said AFABP comprises the amino acid sequence of SEQ ID NO:4 and wherein a reduction in AFABP expression inhibits formation of an atherosclerotic lesion and wherein said compound comprises an nucleic acid comprising 10-100 nucleotides, the sequence of said nucleotides being complementary to a coding sequence of SEQ ID NO:2.

Claim 3 states the method of claim 1, wherein said compound inhibits transcription of said AFABP.

Claim 5 states the method of claim 1, wherein the compound inhibits expression of said AFABP in macrophages but not inadipocytes.

Claim 6 states the method of claim 1, wherein the compound inhibits expression of said AFABP in adipocytes but not in macrophages.

Claim 9 as amended states the method of claim 1, wherein the antisense nucleic acid is a DNA operatively linked to a macrophage-specific promoter, wherein transcription of said DNA

yields nucleic acid product which is complementary to an mRNA encoding an AFABP polypeptide.

Claim 10 states the method of claim 1, wherein said compound is introduced into an artery of said mammal.

Claim 11 states the method of claim 1, wherein said compound is introduced into an artery of said mammal.

Claim 12 as amended states a method of inhibiting differentiation of a macrophage into a foam cell, comprising contacting said macrophage with an inhibitor of AFABP expression, wherein said AFABP comprises the amino acid sequence of SEQ ID NO:4 and wherein a reduction in AFABP expression inhibits differentiation of a macrophage into a foam cell and wherein said compound comprises an nucleic acid comprising 10-100 nucleotides, the sequence of said nucleotides being complementary to a coding sequence of SEQ ID NO:2.

New claim 24 states a method of inhibiting differentiation of a macrophage into a foam cell, comprising contacting said macrophage with an inhibitor of AFABP expression, wherein a reduction in AFABP expression inhibits differentiation of a macrophage into a foam cell and wherein said inhibitor comprises a compound that binds to a cis-acting regulatory sequence of AFABP, said inhibitor comprising a peroxisome proliferator-activated receptor gamma (PPAR gamma) or peroxisome proliferator-activated receptor alpha (PPARalpha) compound.

New claim 25 states a method of inhibiting formation of an atherosclerotic lesion comprising administering to a mammal a compound that reduces expression of AFABP, wherein

said inhibitor comprises a compound that binds to a cis-acting regulatory sequence of AFABP, said inhibitor comprising a peroxisome proliferator-activated receptor gamma (PPARgamma) or peroxisome proliferator-activated receptor alpha (PPARalpha) compound.

The claims remain rejected for the same reasons set forth in the previous Office action mailed 8/14/02. Although the claims 1-3, 5-6 and 9-12 have been amended to state that the inhibitor is a nucleic acid of 10-100 bases that is complementary to instant SEQ ID NO:2, neither the specification nor the prior art taught any such nucleic acids that upon administration to a mammal, as claimed, would have the claimed functions of inhibiting formation of an atherosclerotic lesion. New claims 24 and 25 do not further recite what the inhibitor of AFABP is, and thus remain rejected for the reasons set forth in the previous Official action as well.

Applicants state on page 4 of the response filed 2/14/03 that "[t]he Examiner's rational seems to suggest that methods for using antisense oligonucleotides to inhibit gene expression (or other activities), even if limited to a specific gene target, are not worthy of patent protection because of the difficulties in the field. Although antisense methods may require further experimentation to optimize the desired result of reduced expression of a target gene, the methodology is well established and well accepted by the scientific and medical community. Numerous antisense compositions are currently being administered to human subjects and antisense technology is regarded as a sound therapeutic approach. The enablement standard permits some experimentation, so long as it is not undue. The difficulties described by the

Examiner pertain to the general technology of antisense, rather than the specific invention claimed-- use of AFABP antisense nucleic acids to inhibit tumor growth."

The main emphasis of the references cited in support of the standing enablement rejection was that while design of antisense for use in cells in cell culture is possible for a known target gene, there is a high level of unpredictability in the art for making and using antisense in whole organisms and further where treatment effects might be obtained. There is no specific guidance in either the specification as filed or the prior art to provide one of skill in the art the information needed to overcome the unpredictability in the art cited in the previous Office action. This unpredictability is such that one skilled in the art would necessarily have to engage in and practice trial and error experimentation to discover *de novo* antisense that are able to both target AFABP (SEQ IDNO:2) in a whole mammal and in such a manner as to provide the claimed functions, namely inhibition of atherosclerotic lesions. There is no guidance in the art nor the specification as filed for teaching how to target and effect the claimed functions *in vivo* using antisense as the therapeutic agent.

Applicants further state that "Applicants made a significant contribution to the field of cardiovascular medicine by elucidating a molecular mechanism by which atherosclerotic lesions develop and by identifying a therapeutic target, AFABP. The amended claims are commensurate with the scope of the disclosure and their contribution to the field. Optimization of AFABP oligonucleotides and confirming their inhibitory activity in vivo is well within the skill of a practitioner in the art of antisense technology. Given the description in the specification,

evidence that a reduction in AFABP cooerssion inhibits macrophage differentiation and atherosclerotic lesion formation, and the copious information regarding making and using antisense oligonucleotides known in the art, Applicants submit that undue experimentation is not required to practice the invention as now claimed."

However, applicant has not considered the facts as presented by those skilled in the antisense art in the cited references found in the previous Office action. Those references clearly stated that there is not a known optimization of antisense that will allow antisense to predictably work in a whole organism since antisense functions differently *in vivo* than *in vitro*. As noted in the previous Office action, antisense to one target gene does not allow the determination of the effects of antisense to another target gene. Furthermore, there are numerous examples of attempts to use antisense to a particular target gene in vivo, where there was no success since the right concentration could not be achieved, the antisense was toxic, had too much non-specific binding, or was degraded too quickly prior to location of its target *in vivo*. These unpredictable factors were stated in the previous Office action as being necessary to overcome for the specific target gene and functions desired *in vivo*. Thus, while one of skill in the art might be able to readily find a nucleic acid antisense of 10-100 bases that is able to hybridize to instant SEQ IDNO:2, there is no further guidance taught in either the specification as filed or the prior art for how to administer and use any such antisense for the instant functions claimed, namely inhibition of atherosclerotic lesion.

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

M. M. Schmidt
May 1, 2003